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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
31176282-004001

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on November 27, 2006

Signature /Michael D. Berger/

Typed or printed name Michael D. Berger, Ph.D.

Application Number	Filed
10/820,656	April 8, 2004

First Named Inventor: Schaub, et al.

Art Unit	Examiner
1616	Alstrum-Acevedo

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest
See 37 CFR 3.71. Statement under 37 CFR 3.73 (b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record.
Registration number 52,616

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Registration number if acting under 37 CFR 1.34 _____

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November 27, 2006
Date

NOTE: Signatures of all the investors or assignee of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 7 forms are submitted

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Dear Sirs:

Claims 1-28 are pending in the current patent application. All pending claims stand rejected under 35 U.S.C. §103 based on Lechuga-Ballesteros, et al. (WO0132144), Russell, et al. (2001), and DeFrees, et al. (US20040137557). The claims were first rejected in the Office Action mailed February 21, 2006. After the Applicants' response, the claims were finally rejected on July 27, 2006. Thus, the claims have been twice rejected and are ripe for appeal. Applicants request reconsideration of the final rejection of claims 1-28 in this Pre-Appeal Brief Request for Review because the examiner has failed to present a case of *prima facia* obviousness under 35 U.S.C. §103(a) because the cited art fails to teach every element cited in the pending claims.

COMMENTS REGARDING THE CLAIMED INVENTION

Inventors are the first to specifically demonstrate that F.IX can be both **dried and aerosolized, yet maintain activity**, the first to show systemic delivery of aerosolized F.IX, and the first to show sequestration of aerosolized F.IX allowing treatment in advance of need. Prior to this demonstration, **no one** had successfully treated hemophilia by inhalation therapy because pulmonary delivery of coagulation proteins is hindered by their large size, notorious instability, and denaturation by sheer forces during aerosolization and delivery.[1]

PREVENTATIVE TREATMENT IS PATENTABLE (CLAIMS 14-16)

None of the cited references provide "A method of preventing hemophilic bleeding **in advance** of a hemophilic assault..." with a "**once per week**" application as described in claim 14. Further, none of the cited references provide "bi-weekly" inhalation as described in claim 15 or inhalation "every 2 to 3 days" as described in claim 16.

The pharmacokinetics of inhaled F.IX contrast strongly with those of intravenous F.IX, providing better immediate drug action and longer staying power (see FIG. 8—**compare ~ 400 ng/ml versus ~ 80 ng/ml** at 50 hr). The deposition and sequestration of F.IX in the lungs and

[1] Gupta attempted the pulmonary delivery of coagulation factors, but found that human Factor IX was denatured during nebulization and hypothesized that this was due to shear forces imposed by the nebulizers or the large air water interface produced during the process. Gupta S, et al., Pulmonary delivery of human protein C and Factor IX, in (ed) NaL (ed): Oxygen Transport to Tissue XVIII. New York: Plenum Press 1997; p 429-35.

preventative treatment of hemophilia could not have been developed without determining the *in vivo* bioavailability as described in Example 3, and it was completely **surprising** that the effect would last so long, thus allowing preventative use of the drug. **At the very least, claims 14-16 are patentable over the cited references because none of them teach these unexpected recited features.**

TREATMENT IS NOVEL (CLAIMS 1-7 AND 8-13)

The treatment claims are novel because none of the cited references teach a "method of treating hemophilia... by inhalation ... of aerosolized F.IX." At best the Russell reference shows **intertracheal** administration of **liquid** F.IX, but it does not show **"inhaling"** or **"inhalation"** of the **"aerosolized** F.IX" from a **"dry powder"** as required by claims 1 and 8.

Further, Gupta[2] attempted the pulmonary delivery of coagulation factors, but found that human Factor IX was denatured during nebulization and hypothesized that this was due to shear forces imposed by the nebulizers or the large air water interface produced during the process.

Thus, the art does **not** teach treatment by inhalation of aerosolized F.IX and even **teaches away** from it by suggesting that it is not possible to achieve. **At the very least claims 1-7 and 8-13 are patentable because the cited art fails to teach each of the recited features.**

MONOMER CONTENT IS NOT TAUGHT BY THE CITED REFERENCES

The Examiner withdrew the rejection of anticipation over Lechuga, recognizing that Lechuga fails to teach monomer content, FPF content, and activity. Thus, the claims remain rejected as obvious. However, Examiner has cited to **no art teaching these missing characteristics**, instead relying on the similarity to Lechuga and apparently suggesting the recited characteristics are **inherent** to same. Examiner has even suggested that a direct comparison with the samples of Lechuga be made.

The Examiner, however, cannot make an obviousness case based on inherency; inherency is for anticipation not obviousness. *In re Rijckaert,* 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("That which may be inherent is not necessarily known. **Obviousness cannot be predicated on what is unknown**.") (citations omitted).

Further, Applicants clearly identify F.IX **stability as a problem** due to the large size of the complex:

> "[N]o one has succeeded in the pulmonary delivery of coagulation proteins, presumably due to their large size and their notorious instability in solution." ¶19

The specification describes use of a "dry powder aerosolized formulation, in an attempt to **minimize the expected instability**." (¶59). "Several techniques were used to analyze samples for aggregation and degradation." (¶78). "UV spectrophotometric analyses were used to evaluate turbidity (aggregation/precipitation) in samples." (¶79).

The limitations described in the claims, namely **monomer content, FPF, and activity** are a **measure of protein stability** and are required to provide stable, deliverable, active aerosolized F.IX. Because the cited references **do not** even produce aerosolized F.IX it certainly cannot be said that the missing characteristics are "necessarily present." Therefore, claims 1-28, each reciting monomer content, FPF content and activity level, are all patentable over the cited art.

Applicants provide a chart comparing claim 1 (as an exemplary claim) to the cited art. It is immediately apparent that the cited art fails to show treatment using aerosolized F.IX. Further, one cannot assume the that cited monomer content, FPF content and activity levels are "necessarily present" in Lechuga.[3]

Table 1: differences between the claimed invention and the prior art

Instant Invention—Sample claim	Lechuga	Russell	DeFrees
claim 1 (original). a method of treating hemophilia, said method comprising	not present	present	present
a) aerosolizing a factor ix (F.IX)	spray dried F.IX	liquid F.IX	intravenous
wherein the aerosolized F.IX:	not present	not present	not present
i) has a mass median aerodynamic diameter (MMAD) of between 2 and 4 μm,	present	not present	not present
has a fine particle fraction percent less than 3.3 μm (FPF % < 3.3μm) of at least 50%	not described	not present	not present
ii) is at least 90% monomeric,	not described	not present	not present

[2] Gupta S, et al., Pulmonary delivery of human protein C and Factor IX, in (ed) NaL (ed): Oxygen Transport to Tissue XVIII. New York: Plenum Press 1997; p 429-35.

[3] See MPEP 2112 ("The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because **inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art**); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is **necessarily present** in the thing described in the reference...Inherency, however, may not be established by probabilities or possibilities...") (emphasis added).

Table 1: differences between the claimed invention and the prior art

Instant Invention—Sample claim	Lechuga	Russell	DeFrees
iii) wherein the after-aerosolization activity/pre-aerosolization activity is at least 80%; and	not described	not present	not present
is a dry powder having less than 10% water (wt/wt);	not described	not present	not present
b) inhaling the aerosolized F.IX and	not described	**intertracheal** placement, **not** inhalation	not present
allowing the aerosolized F.IX to deposit in the lung;	not described	not present	not present
c) followed by exhalation.	not described	present	present

OBVIOUSNESS-TYPE DOUBLE PATENTING

The issued claims in US Application 10/313,343 (now U.S. Patent No. 6,835,372) and 10/985,509 (pending) are directed to compositions comprising an active agent and a di- or tri-peptide and/or methods of administering such compositions. The issued and pending claims of these matters do not recite aerosolized F.IX, treatment with such F.IX, preventative treatment with such F.IX, or the recited monomer, FPF, and activity levels. US Applications 10/313,343 and 10/985,509 fail to establish obviousness-type double patenting because they **do not teach** or suggest all of the claim limitations.

CONCLUSION

Applicants believe that the claims are in condition for allowance and respectfully request that the Examiners grant such an action.

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Respectfully Submitted

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